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CLINICAL STUDY

Decrement of postprandial insulin secretion determines the progressive nature of type-2 diabetes

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Abstract

Objective: Type-2 diabetes is a progressive disease. However, little is known about whether decreased fasting or postprandial pancreatic β-cell responsiveness is more prominent with increased duration of diabetes. The aim of this study was to evaluate the relationship between insulin secretion both during fasting and 2 h postprandial, and the duration of diabetes in type-2 diabetic patients.
Design: Cross-sectional clinical investigation.
Methods: We conducted a meal tolerance test in 1466 type-2 diabetic patients and calculated fasting (M_0) and postprandial (M_1) β-cell responsiveness.
Results: The fasting C-peptide, postprandial C-peptide, M_0, and M_1 values were lower, but HbA_{1c} values were higher, in patients with diabetes duration $>$ 10 years than those in other groups. There was no difference in the HbA_{1c} levels according to the tertiles of their fasting C-peptide level. However, in a group of patients with highest postprandial C-peptide tertile, the HbA_{1c} values were significantly lower than those in other groups. After adjustment of age, sex, and body mass index (BMI), the duration of diabetes was found to be negatively correlated with fasting C-peptide ($\gamma = -0.102$), postprandial C-peptide ($\gamma = -0.356$), M_0 ($\gamma = -0.263$), and M_1 ($\gamma = -0.315$; $P<0.01$ respectively). After adjustment of age, sex, and BMI, HbA_{1c} was found to be negatively correlated with postprandial C-peptide ($\gamma = -0.264$), M_0 ($\gamma = -0.379$), and M_1 ($\gamma = -0.522$), however, positively correlated with fasting C-peptide ($\gamma = 0.105$; $P<0.01$ respectively). In stepwise multiple regression analysis, M_0, M_1, and homeostasis model assessment for insulin resistance (HOMA-IR) emerged as predictors of HbA_{lc} after adjustment for age, sex, and BMI ($R^2 = 0.272$, 0.080, and 0.056 respectively).
Conclusions: With increasing duration of diabetes, the decrease of postprandial insulin secretion is becoming more prominent, and postprandial β-cell responsiveness may be a more important determinant for glycemic control than fasting β-cell responsiveness.

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Introduction

A variety of oral glucose and meal tolerance tests have extensively been used to diagnose type-2 diabetes mellitus in a clinical setting. The oral load results in a typical postprandial exposure of the pancreas to glucose, nutrient (protein and fat), and gut and vagal hormones. The measurement of pancreatic responsiveness, therefore, closely reflects the ability of the pancreas to produce insulin under normal physiological conditions (1).

The results of United Kingdom Prospective Diabetes Study indicate that, in the group with intensive treatment, it took 6 and 4 years before the fasting plasma glucose level and HbA_{1c} returned to the pretherapy level respectively, and the difference may reflect increasing postprandial hyperglycemia (2). Relative contribution of fasting and postprandial plasma glucose to the HbA_{1c} remains to be uncertain; some researchers support fasting plasma glucose values to be a better predictor for the overall glycemia as reflected by the HbA_{1c} value (3), whereas others favor postprandial plasma glucose as a better predictor (4–6). Results from studies aimed at reducing postprandial glycemia support the latter claim (7, 8). Therefore, postprandial glucose concentration appears to contribute more or at least equally to the overall glycemia than fasting glucose concentration. Furthermore, decreased postprandial insulin response most plausibly explains elevated fasting plasma glucose, HbA_{1c}, and glucose responses to meal in newly presenting type-2 diabetic patients (9).

Todate, most studies on the β-cell function in type-2 diabetes had some limitations: (i) only fasting insulin secretion was measured (2), or (ii) postprandial insulin secretion was measured in a small number of patients

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(9). There have been few studies on the association of fasting and postprandial 2-h insulin secretion with the duration of diabetes and glycemic control in a large number of type-2 diabetic patients, whose durations of diabetes are varied. Therefore, we undertook to examine the relationship of insulin secretion during fasting and postprandial 2 h with the duration of diabetes and glycemic control in Korean type-2 diabetic patients.

Subjects and methods

Study subjects

Randomly selected type-2 diabetic patients ($n=1466$, 810 males and 656 females), who visited the Diabetes Center at Severance Hospital, Yonsei University Medical Center from June 2002 to April 2005 for glycemic control were enrolled in this study. Their treatment methods were not changed during the last 3 months. Patients presenting with symptoms suggestive of type-1 diabetes, defined as diabetic ketoacidosis, acute presentation with heavy ketonuria (3+), or continuous requirement of insulin within 1 year of diagnosis were excluded. Patients with glutamic acid decarboxylase antibody positivity were excluded. Patients who had taken steroid or renal impairment (plasma Cr higher than 1.5 mg/dl) were also excluded. Furthermore, 54 patients with insulin treatment were also included. The insulin concentration data on patients with insulin treatment were excluded from the analysis. The Ethics Committee of Yonsei University College of Medicine, Seoul, approved this study, and informed consent was obtained from each subject.

Methods

Subjects' height and weight were measured to the nearest 0.1 cm and 0.1 kg respectively. They were allowed to wear light clothing but not to wear shoes. Body mass index (BMI) was calculated as weight (kg) over the square of the height (m^2). Blood samples were collected after 12-h fasting. Fasting glucose was measured by the glucose oxidase method. HbA_{1c} was analyzed by HPLC (Variant II; Bio-Rad; coefficient of variation (CV)=2.1%). Insulin concentration was measured by IRMA (RIABEAD II kit, Abbott, Japan; intra-assay CV 1.2–1.9%, inter-assay CV 1.4–3.3%). The concentration of C-peptide was measured by RIA (DiaSorin, Stillwater, MN, USA; CV=2.7%).

After obtaining fasting blood samples, patients were allowed to eat one type of meal selected from a few standardized meals (total 823 ± 132 kcal containing, protein 17.7 ± 4.6%, fat 16.3 ± 6.4%, and carbohydrate 65.9 ± 10.0%), while medications were taken as usual. The concentration of serum glucose, insulin, and C-peptide was measured 2 h after the meal. Currently used oral hypoglycemic agents were examined: one tablet of sulfonylurea was considered as 80 mg gliclazide or 2 mg glimepiride (10), and one tablet of biguanide was considered as 500 mg metformin. With regard to α-glucosidase inhibitor, 0.2 mg voglibose were considered to be equivalent to 100 mg acarbose (11). Rosiglitazone (4 mg) and pioglitazone (15 mg) were considered to be equivalent (12, 13).

Δ Insulin concentration was defined as the postprandial 2-h insulin concentration minus fasting insulin concentration, and Δ C-peptide concentration as the postprandial 2-h C-peptide concentration minus fasting C-peptide concentration.

Fasting β-cell responsiveness (M_0) represents the ability of fasting glucose to stimulate β-cell secretion (1) and postprandial β-cell responsiveness (M_1) represents the ability of postprandial glucose to step up β-cell secretion (1), and they were calculated using the formula of Hovorka *et al.* (1) with some modification:

$$M_0 = 100 \times \text{fasting C-peptide (μg/l)/fasting glucose concentration (mg/dl)}$$

$$M_1 = 100\,(\text{postprandial 2-h C-peptide concentration (μg/l)} - \text{fasting C-peptide concentration (μg/l)})/(\text{postprandial 2-h glucose concentration (mg/dl)} - \text{fasting glucose concentration (mg/dl)})$$

As an indicator of insulin resistance, this study used the homeostasis model assessment for insulin resistance (HOMA-IR), which was calculated as follows (14):

$$\text{HOMA-IR} = (\text{fasting insulin (μU/ml)} \times \text{fasting glucose (mmol/l)}/22.5)$$

According to the duration of diabetes, the subjects were divided into three groups; shorter than 5 years, from 5 years to less than 10 years, and longer than 10 years for analysis. According to their fasting, postprandial and Δ C-peptide concentrations, the subjects were divided into three groups. After adjustment for age, sex, and BMI, the correlation between duration of diabetes, HbA_{1c}, and other metabolic parameters was analyzed.

Statistical analysis

Statistical analyses were performed using SPSS software (version 13.0; SPSS, Inc., Chicago, IL, USA). All continuous variables are expressed as mean ± S.D., except insulin, C-peptide, HOMA-IR, M_0, and M_1, which are described as median and range and were log-transformed to accommodate skewing of the distribution. Comparisons between groups classified by the duration of diabetes, fasting C-peptide, postprandial C-peptide, and Δ C-peptide value were performed by using ANOVA followed by *post hoc* testing

with Tukey's test. The χ^2 test was used for categorical variables. Partial Pearson's correlation coefficiency between the duration of diabetes and HbA_{1c}, and other metabolic parameters were preformed after adjustment of age, sex, and BMI. Stepwise multiple regression analysis with HbA_{1c} as a dependent variable was performed. Variables of age, gender, BMI, M_0, M_1, and HOMA-IR were analyzed as independent variables. A two-sided value of $P<0.05$ was considered to be statistically significant.

Results

Clinical characteristics of patients

The mean age of patients was 55.0 ± 11.5 years, the mean duration of diabetes was 5.0 ± 5.7 years, mean BMI was 25.4 ± 3.2 kg/m^2, and the median concentrations of fasting, postprandial, and Δ C-peptide were 1.54 (0.54–6.70) μg/l, 3.74 (1.01–17.63) μg/l, and 2.11 (0.01–14.84) μg/l respectively.

Clinical characteristics according to the duration of diabetes

In the group with diabetes for longer than 10 years, their age, and HbA_{1c} value were higher, and their BMI, fasting C-peptide, postprandial C-peptide, fasting insulin, postprandial insulin, Δ insulin, Δ C-peptide, fasting β-cell responsiveness, and postprandial β-cell responsiveness were lower than those in other groups. The number of tablets of sulfonylurea, metformin, α-glucosidase inhibitor, and thiazolidinedione used were higher than those in the group with diabetes for less than 5 years. Furthermore, the prevalence of patients with insulin treatment was higher (Table 1).

Clinical characteristics according to the tertiles of fasting C-peptide level

In the group with highest fasting C-peptide tertile, their duration of diabetes was shortest. Their BMI, fasting insulin, postprandial insulin, postprandial C-peptide, Δ insulin, Δ C-peptide, fasting β-cell responsiveness, and postprandial β-cell responsiveness were higher than those of other groups. However, the concentrations of fasting glucose, postprandial glucose, and HbA_{1c} were not different among the three groups (Table 2).

Clinical characteristics according to the tertiles of postprandial C-peptide level

In the group with highest postprandial C-peptide tertile, their duration of diabetes was shorter, and their BMI, fasting insulin, postprandial insulin, fasting C-peptide, Δ insulin, Δ C-peptide, fasting β-cell responsiveness, and postprandial β-cell responsiveness were higher than those of the other two groups. However, the

Table 1 Clinical characteristics according to the duration of diabetes. Data are expressed as mean ± S.D. Insulin, C-peptide, M_0, and M_1 values are described as median (range) values.

Duration of diabetes (years)	**<5**	**≥5–<10**	**≥10**
n	887	240	339
Age (years)	52.3±11.9	55.8±10.1*	59.9±9.6†‡
Sex (female %)	42	48	48
BMI (kg/m^2)	25.7±3.3	25.3±2.9	24.5±3.0†‡
Fasting glucose (mmol/l)	7.50±2.09	8.63±2.38*	8.93±2.59†
PP 2-h glucose (mmol/l)	11.54±4.24	13.76±4.18*	14.32±4.53†
HbA_{1c} (%)	7.5±1.6	8.0±1.5*	8.4±1.5†‡
Fasting insulin (pmol/l)	51.1 (4.8–234.8)	50.3 (10.0–212.5)	42.5 (8.4–225.7)†‡
PP 2-h insulin (pmol/l)	267.1 (17.7–2152.5)	194.2 (26.3–1123.1)*	150.2 (20.0–900.2)†‡
Fasting C-peptide (μg/l)	1.60 (0.69–5.70)	1.56 (0.70–6.70)	1.39 (0.54–3.72)†‡
PP 2-h C-peptide (μg/l)	4.21 (1.03–17.63)	3.43 (1.27–14.69)*	2.90 (1.01–8.50)†‡
Δ Insulin (pmol/l)	210.9 (2.7–1972.2)	144.4 (7.3–984.5)*	103.5 (0.5–760.4)†‡
Δ C-peptide (μg/l)	2.50 (0.02–14.84)	1.88 (0.05–7.99)*	1.49 (0.01–7.22)†‡
M_0	1.25 (0.35–6.79)	1.02 (0.42–3.99)*	0.91 (0.27–3.14)†‡
M_1	3.30 (−481.0–372.0)	1.88 (−252.0–67.7)*	1.42 (−81.0–53.3)†‡
HOMA-IR	2.27 (0.31–16.54)	2.42 (0.33–16.66)	2.17 (0.40–12.06)
No. of tablet of sulfonylurea	0.18±0.39	0.83±0.68*	1.16±0.87†‡
No. of tablet of metformin	0.70±1.01	1.46±1.21*	1.37±1.21†
No. of tablet of AGL	0.09±0.43	0.47±1.16*	0.57±1.10†
No. of tablet of TZD	0.05±0.19	0.16±0.37*	0.16±0.35†
No. of tablet of other OHA	0.04±0.29	0.02±0.27	0.08±0.45
Prevalence of insulin user (%)	0.2	2.5	13.6†‡

BMI, body mass index; PP, postprandial; M_0, fasting β-cell responsiveness; M_1, postprandial β-cell responsiveness; AGL, α-glucose inhibitor; TZD, thiolidinedione; OHA, oral hypoglycemic agents; HOMA-IR, homeostatic model assessment of insulin resistance. *P* value was obtained from the ANOVA (*post hoc* and Tukey's test). *$P<0.05$ between groups (duration of diabetes below 5 years versus duration of diabetes above 5 years and below 10 years). †$P<0.05$ between groups (duration of diabetes below 5 years versus duration of diabetes above 10 years). ‡$P<0.05$ between groups (duration of diabetes above 5 years and below 10 years versus duration of diabetes above 10 years).

Table 2 Clinical characteristics according to the tertile of fasting C-peptide level. Data are expressed as mean ± S.D. Insulin, C-peptide, M_0, and M_1 values are described as median (range) values.

Tertile of fasting C-peptide	Tertile 1	Tertile 2	Tertile 3
n	489	493	484
C-peptide range (μg/l)	0.54–1.33	1.34–1.83	1.84–6.70
Age (years)	56.0 ± 10.7	55.1 ± 11.5	54.0 ± 12.1†
Sex (female %)	50	42*	43
Duration of diabetes (years)	6.3 ± 6.5	5.0 ± 5.6*	3.7 ± 4.6†‡
BMI (kg/m^2)	24.1 ± 2.8	25.3 ± 2.9*	26.7 ± 3.3†‡
Fasting glucose (mmol/l)	7.85 ± 2.51	8.12 ± 2.30	8.08 ± 2.21
PP 2-h glucose (mmol/l)	12.38 ± 4.71	12.56 ± 4.40	12.66 ± 4.31
HbA_{1c} (%)	7.7 ± 1.6	7.8 ± 1.6	7.9 ± 1.5
Fasting insulin (pmol/l)	28.6 (4.8–219.0)	46.2 (8.8–153.5)*	74.4 (10.9–234.8)†‡
PP 2-h insulin (pmol/l)	158.4 (17.7–1123.1)	211.6 (25.8–1486.1)*	326.4 (25.6–2152.5)†‡
PP 2-h C-peptide (μg/l)	2.86 (1.01–10.70)	3.57 (1.39–9.54)*	5.19 (2.07–17.63)†‡
Δ Insulin (pmol/l)	120.5 (0.9–984.5)	160.5 (0.5–1411.9)*	251.1 (0.9–1972.2)†‡
Δ C-peptide (μg/l)	1.79 (0.01–9.70)	2.03 (0.05–7.81)*	2.73 (0.02–14.84)†‡
M_0	0.80 (0.27–1.74)	1.14 (0.56–2.53)*	1.71 (0.75–6.79)†‡
M_1	1.94 (−252.0–176.5)	2.24 (−161.5–372.0)	3.11 (−481.0–332.0)†‡
HOMA-IR	1.36 (0.31–9.11)	2.24 (0.31–10.77)*	3.64 (0.35–16.66)†‡
No. of tablet of sulfonylurea	0.47 ± 0.63	0.49 ± 0.65	0.44 ± 0.64
No. of tablet of metformin	1.02 ± 1.13	1.03 ± 1.13	0.87 ± 1.15
No. of tablet of AGL	0.27 ± 0.76	0.25 ± 0.73	0.24 ± 0.74
No. of tablet of TZD	0.15 ± 0.31	0.07 ± 0.22*	0.07 ± 0.23*
No. of tablet of other OHA	0.04 ± 0.30	0.04 ± 0.29	0.05 ± 0.36
Prevalence of insulin user (%)	6.7	2.8*	1.4*

BMI, body mass index; PP, postprandial; M_0, fasting β-cell responsiveness; M_1, postprandial β-cell responsiveness; HOMA-IR, homeostatic model assessment of insulin resistance; AGL, α-glucose inhibitor; TZD, thiolidinedione; OHA, oral hypoglycemic agents. *P* value was obtained from the ANOVA (*post hoc* and Tukey's test). *$P<0.05$ between groups (tertile 1 versus tertile 2). †$P<0.05$ between groups (tertile 1 versus tertile 3). ‡$P<0.05$ between groups (tertile 2 versus tertile 3).

concentrations of fasting glucose and HbA_{1c} were lower than those of other groups, although they used the lowest dosage of sulfonylurea and metformin among the three groups. The prevalence of patients with insulin treatment was lower (Table 3).

Clinical characteristics according to the tertiles of Δ C-peptide level

In the group with highest Δ C-peptide tertile, subjects' duration of diabetes was shorter, and their BMI, fasting insulin, postprandial insulin, fasting C-peptide, postprandial C-peptide, Δ insulin, fasting β-cell responsiveness, and postprandial β-cell responsiveness were higher than those of the other two groups. However, the concentrations of fasting glucose, postprandial glucose, and HbA_{1c} were lower than those of the other groups, although they used the lowest dosage of sulfonylurea and metformin among the three groups. The prevalence of patients with insulin treatment was lower (Table 4).

The distribution of C-peptide according to the duration of diabetes

The distribution of fasting C-peptide, postprandial C-peptide, and Δ C-peptide concentrations according to the duration of diabetes were shown in Fig. 1A–C respectively.

Relationship between the duration of diabetes and other metabolic parameters

After adjustment of age, sex, and BMI, the duration of diabetes was found to be negatively correlated with fasting insulin ($\gamma=-0.098$), postprandial insulin ($\gamma=-0.315$), fasting C-peptide ($\gamma=-0.102$), postprandial C-peptide ($\gamma=-0.356$), Δ insulin ($\gamma=-0.309$), Δ C-peptide ($\gamma=-0.358$), fasting β-cell responsiveness ($\gamma=-0.263$), and postprandial β-cell responsiveness ($\gamma=-0.315$), but positively with fasting glucose ($\gamma=0.272$), postprandial glucose ($\gamma=0.241$), and HbA_{1c} ($\gamma=0.210$) ($P<0.001$, except for fasting insulin $P<0.01$).

Relationship between HbA_{1c} and other metabolic parameters

After adjustment of age, sex, and BMI, HbA_{1c} was found to be positively correlated with the duration of diabetes ($\gamma=0.210$), fasting glucose ($\gamma=0.704$), postprandial glucose ($\gamma=0.685$), and fasting C-peptide ($\gamma=0.105$), but negatively with postprandial insulin ($\gamma=-0.294$), postprandial C-peptide ($\gamma=-0.264$), δ insulin ($\gamma=-0.306$), Δ C-peptide ($\gamma=-0.352$), fasting β-cell responsiveness ($\gamma=-0.379$), and postprandial β-cell responsiveness ($\gamma=-0.522$; $P<0.001$). However, correlation with fasting insulin concentration was not significant.

Table 3 Clinical characteristics according to the tertile of postprandial 2-h C-peptide level. Data are expressed as mean ± S.D. Insulin, C-peptide, M_0, and M_1 values are described as median (range) values.

Tertiles of PP 2-h C-peptide	Tertile 1	Tertile 2	Tertile 3
n	481	493	492
C-peptide range (μg/l)	1.01–3.11	3.12–4.45	4.46–17.63
Age (years)	55.2 ± 11.0	55.1 ± 11.0	54.8 ± 12.3
Sex (female %)	47	44	43
Duration of diabetes (years)	7.5 ± 6.5	4.8 ± 5.4*	2.8 ± 4.0†‡
BMI (kg/m^2)	24.3 ± 3.0	25.5 ± 3.1*	26.3 ± 3.2†‡
Fasting glucose (mmol/l)	8.84 ± 2.76	7.95 ± 2.09*	7.28 ± 1.84†‡
PP 2-h glucose (mmol/l)	13.28 ± 4.95	12.51 ± 4.42*	11.87 ± 3.92†
HbA_{1c} (%)	8.3 ± 1.8	7.7 ± 1.5*	7.4 ± 1.4†‡
Fasting insulin (pmol/l)	34.3 (4.8–153.5)	46.9 (9.9–219.0)*	62.7 (11.3–234.8)†‡
PP 2-h insulin (pmol/l)	114.6 (17.7–528.3)	225.6 (42.8–790.0)*	408.4 (46.0–2152.5)†‡
Fasting C-peptide (μg/l)	1.22 (0.54–2.91)	1.53 (0.70–3.91)*	2.10 (0.82–6.70)†‡
Δ Insulin (pmol/l)	76.1 (0.5–448.2)	177.8 (4.6–619.2)*	341.6 (3.6–1972.2)†‡
Δ C-peptide (μg/l)	1.09 (0.01–2.27)	2.14 (0.02–3.51)*	3.69 (0.70–14.84)†‡
M_0	0.81 (0.27–2.84)	1.12 (0.43–3.12)*	1.59 (0.48–6.79)†‡
M_1	1.09 (−88.0 to 63.5)	2.25 (−252.0–167.0)*	4.56 (−481.0–372.0)†‡
HOMA-IR	1.76 (0.31–10.77)	2.25 (0.38–16.54)*	2.75 (0.49–16.66)†‡
No. of tablet of sulfonylurea	0.64 ± 0.74	0.51 ± 0.66	0.29 ± 0.49†‡
No. of tablet of metformin	1.21 ± 1.26	1.03 ± 1.13	0.68 ± 1.00†‡
No. of tablet of AGL	0.33 ± 0.84	0.27 ± 0.78	0.16 ± 0.60
No. of tablet of TZD	0.11 ± 0.28	0.10 ± 0.26	0.07 ± 0.23
No. of tablet of other OHA	0.03 ± 0.25	0.04 ± 0.30	0.06 ± 0.38
Prevalence of insulin user (%)	8.7	1.8*	0.6†

BMI, body mass index; PP, postprandial; M_0, fasting β-cell responsiveness; M_1, postprandial β-cell responsiveness; HOMA-IR, homeostatic model assessment of insulin resistance; AGL, α-glucose inhibitor; TZD, thiolidinedione; OHA, oral hypoglycemic agents. *P* value was obtained from the ANOVA (*post hoc* and Tukey's test). *$P<0.05$ between groups (tertile 1 versus tertile 2). †$P<0.05$ between groups (tertile 1 versus tertile 3). ‡$P<0.05$ between groups (tertile 2 versus tertile 3).

Table 4 Clinical characteristics according to the tertile of Δ C-peptide level. Data are expressed as mean ± S.D. Insulin, C-peptide, M_0, and M_1 values are described as median (range) values.

Tertiles of Δ C-peptide	Tertile 1	Tertile 2	Tertile 3
n	488	491	487
C-peptide range (μg/l)	0.01–1.59	1.60–2.70	2.71–14.84
Age (years)	54.4 ± 11.2	55.5 ± 11.3	54.8 ± 12.3
Sex (female %)	47	44	43
Duration of diabetes (years)	7.3 ± 6.4	5.1 ± 5.6*	2.8 ± 4.0†‡
BMI (kg/m^2)	24.7 ± 3.2	25.3 ± 3.0*	26.3 ± 3.2†‡
Fasting glucose (mmol/l)	9.04 ± 2.65	7.97 ± 2.16*	7.28 ± 1.84†‡
PP 2-h glucose (mmol/l)	13.54 ± 4.87	12.56 ± 4.58*	11.87 ± 3.92†‡
HbA_{1c} (%)	8.5 ± 1.7	7.7 ± 1.5*	7.4 ± 1.4†‡
Fasting insulin (pmol/l)	42.1 (4.8–192.4)	45.0 (10.0–234.8)*	55.2 (9.9–228.3)†‡
PP 2-h insulin (pmol/l)	117.7 (20.0–503.5)	216.8 (17.7–907.2)*	407.5 (46.0–2152.5)†‡
Fasting C-peptide (μg/l)	1.39 (0.54–5.12)	1.51 (0.70–5.70)*	1.84 (0.76–6.70)†‡
PP 2-h C-peptide (μg/l)	2.48 (1.01–5.82)	3.65 (2.50–8.05)*	5.58 (3.53–17.63)†‡
Δ insulin (pmol/l)	74.3 (0.5–398.5)	168.0 (2.7–795.9)*	344.0 (3.6–1972.2)†‡
M_0	0.90 (0.27–3.21)	3.65 (2.50–8.05)*	1.45 (0.48–4.42)†‡
M_1	1.00 (−88.0–63.5)	2.18 (0.3–16.7)*	4.77 (−481.0–372.0)†‡
HOMA-IR	2.29 (0.31–16.54)	2.18 (0.33–16.66)	2.38 (0.38–10.80)
No. of tablet of sulfonylurea	0.65 ± 0.76	0.48 ± 0.63*	0.27 ± 0.47†‡
No. of tablet of metformin	1.20 ± 1.27	1.01 ± 1.12	0.72 ± 0.98†‡
No. of tablet of AGL	0.36 ± 0.89	0.23 ± 0.74	0.15 ± 0.57
No. of tablet of TZD	0.09 ± 0.26	0.12 ± 0.29	0.07 ± 0.22
No. of tablet of other OHA	0.04 ± 0.29	0.03 ± 0.25	0.07 ± 0.39
Prevalence of insulin user (%)	9	1.0*	1.0†

BMI, body mass index; PP, postprandial; M_0, fasting β-cell responsiveness; M_1, postprandial β-cell responsiveness; HOMA-IR, homeostatic model assessment of insulin resistance; AGL, α-glucose inhibitor; TZD, thiolidinedione; OHA, oral hypoglycemic agents. *P* value was obtained from the ANOVA (*post hoc* and Tukey's test). *$P<0.05$ between groups (tertile 1 versus tertile 2). †$P<0.05$ between groups (tertile 1 versus tertile 3). ‡$P<0.05$ between groups (tertile 2 versus tertile 3).

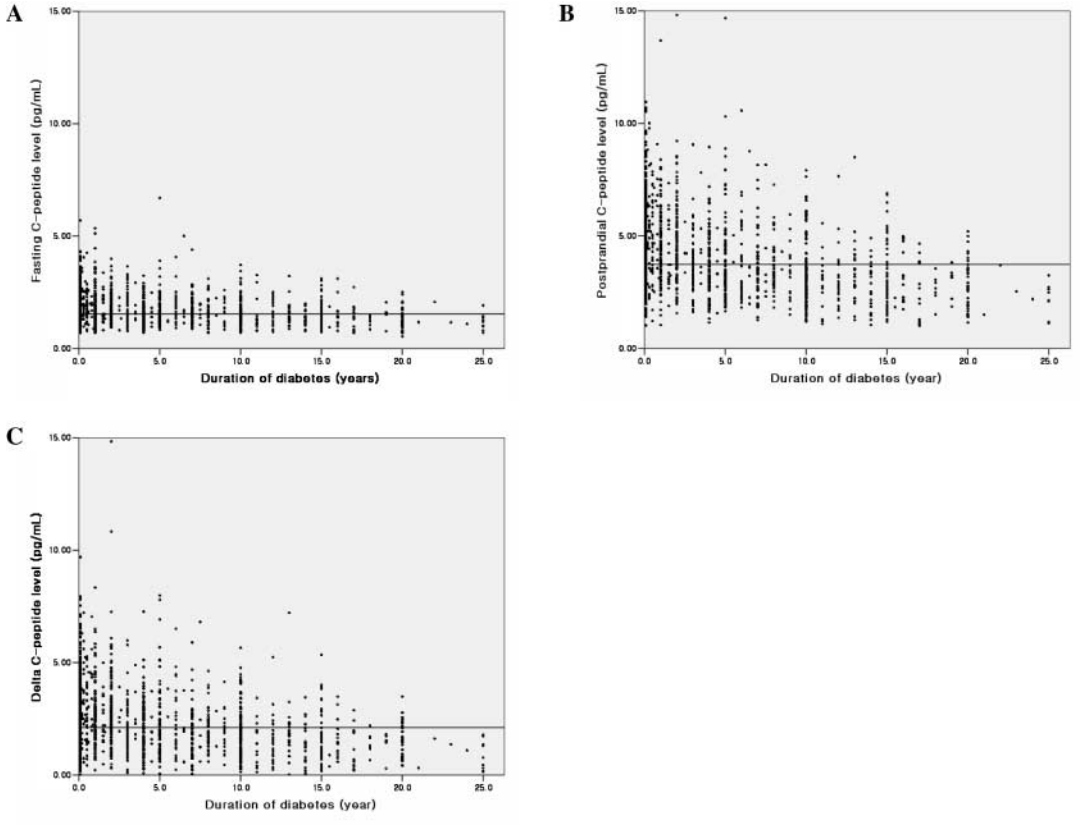

Figure 1 The distribution of C-peptide levels according to the duration of diabetes. (A) Fasting C-peptide, (B) postprandial 2-h C-peptide, and (C) Δ C-peptide. Δ C-peptide concentration was defined as the postprandial 2-h C-peptide concentration minus fasting C-peptide concentration. Horizontal lines indicate the median value of fasting C-peptide, postprandial 2-h C-peptide, and Δ C-peptide level respectively.

Multiple regression analysis with HbA_{1c} as a dependent variable

In stepwise multiple regression analysis, M_0, M_1, and HOMA-IR emerged as predictors of HbA_{1c}. When M_1 was used as a predictor of HbA_{1c}, R^2 was 0.272. When M_1 and HOMA-IR were used as predictors of HbA_{1c}, R^2 was 0.328. When M_1, HOMA-IR, and M_0 were used as predictors of HbA_{1c}, R^2 was 0.408. M_1 explained 27.2% of the variation in the change of HbA_{1c}. The addition of HOMA-IR to M_1 explained an additional 5.6% of the variation in the change of HbA_{1c}. The addition of M_0 to M_1 and HOMA-IR explained an additional 8% of the variation in the change of HbA_{1c} than M_1 plus HOMA-IR.

Discussion

Failure of pancreatic β-cells to secrete adequate insulin to maintain normoglycemia is a prerequisite in the development of type-2 diabetes. Therefore, it is important to evaluate pancreatic β-cell function, which may be a good index of predicting glycemic control and prognosis. The meal tolerance test is more physiological test to measure the pancreatic β-cell function, and it can also distinguish the diverse range response of pancreas (1).

The present results showed that fasting C-peptide, Δ C-peptide, postprandial C-peptide, fasting β-cell responsiveness, and postprandial β-cell responsiveness were decreased, but fasting glucose, postprandial glucose, and HbA_{1c} values were increased with the increase of the duration of diabetes. These results indicate that fasting and postprandial β-cell functions and the degree of glycemic control have deteriorated with the duration of diabetes in type-2 diabetic patients, indicating type-2 diabetes is a progressive disease as shown in the previous study (2). In type-2 diabetic patients, β-cell function assessed by the HOMA method deteriorated in subjects on diet therapy. In subjects on continuing sulfonylurea therapy, β-cell function assessed by the HOMA method increased in the first year but subsequently decreased at 6 years (2). Furthermore, fasting and postprandial 1-h C-peptide levels decreased significantly with the duration of diabetes in type-2 diabetic patients (15).

Our result showed that postprandial insulin secretion was decreased with the increase in the duration of diabetes is in good agreement with those studies with type-1 diabetes (16). Among 2432 patients diagnosed as type-1 diabetes after the age of 18 years, the patients with 1–5 years duration at the time of eligibility screening, stimulated C-peptide was $\geq$0.2 nmol/l in 48% of the cases and $>$ 0.5 nmol/l in 15% of the cases; whereas for those with $>$5–15 years duration, stimulated C-peptide was $\geq$0.2 nmol/l in 8% and $>$0.5 nmol/l in 2% of the cases (16).

In a study for the prevention of type-1 diabetes, it was found no fall of C-peptide (peak and area under the curve) production over time in non-progressors, compared with progressors, regardless of type of tolerance testing employed (mixed meal, oral, or i.v.) (17). These results suggest that the preservation of C-peptide production in the prediabetic period appears to indicate non-progression to clinical disease and may serve as a new surrogate for determining response to preventative efforts. Based on the earlier descriptions, postprandial C-peptide level seems to be used as a progression marker of diabetes not only for the group with high risk of diabetes and type-1 diabetes, but also for the group with type-2 diabetes.

The results of this study showed that the decrease of postprandial C-peptide and β-cell responsiveness, which represent postprandial β-cell function, was more prominent than fasting C-peptide and β-cell responsiveness with the increase of the duration of diabetes. These results are consistent with the results obtained with the newly presenting type-2 diabetic patients (9). The postprandial β-cell responsiveness was reduced by about 80% compared with BMI-matched healthy subjects, whereas fasting β-cell responsiveness was reduced by approximately 50% in the newly presenting type-2 diabetic subjects. Taken together, these results suggest that the reduction of postprandial β-cell responsiveness was more prominent than fasting β-cell responsiveness not only in the early stage of type-2 diabetes, but also in the late stage of type-2 diabetes.

In this study, HbA_{1c} value of patients with the highest tertile of postprandial C-peptide value was significantly lower than in other groups although they had taken the lowest amount of oral hypoglycemic agents, which is consistent with the study on type-1 diabetes mellitus (18). Patients whose C-peptide levels were increased to over 0.20 pmol/ml had better metabolic control, and their HbA_{1c} and fasting and postprandial glucose values were lower although they received less insulin. Furthermore, C-peptide values as low as 0.10–0.20 pmol/ml may also have an impact on diabetic management, since patients in this group required less exogenous insulin to achieve the same level of glycemic control, as those whose stimulated levels were 0.05 pmol/ml or less (18). In other words, even though insulin-secretory capacity is absolutely decreased in type-1 diabetes, peak postprandial C-peptide concentration is important for glycemic control.

In this study, although HbA_{1c} was correlated with both fasting and postprandial β-cell responsiveness, it was more closely correlated with postprandial β-cell responsiveness. Indeed, postprandial insulin deficiency is the most plausible factor underlying elevated fasting plasma glucose, HbA_{1c} and glucose responses to meal in newly presenting type-2 diabetic patients (9), implying that the postprandial β-cell responsiveness is the most important factor in glycemic control not only in the newly presenting diabetic patients, but also in the patients with diverse durations of diabetes.

Type-2 diabetes is characterized by defects in both insulin secretion and insulin sensitivity (19). While hyperglycemia can result from both insulin resistance and β-cell dysfunction, there has been much debate over the past few decades regarding the relative importance of these two abnormalities in the development of type-2 diabetes (20–23). In this study, M_1 and M_0 explained 27.2 and 8.0% respectively, of the variation in the chance of HbA_{1c}, while HOMA-IR explained 5.6% of variation. These results suggest that, although insulin resistance is a crucial factor in glycemic control, insulin secretion, especially postprandial β-cell responsiveness, may be more important in the regulation of glycemic control than insulin resistance. However, since there are various ethnic differences in insulin resistance and β-cell function (24), more studies are required to assess the role of insulin secretion, postprandial β-cell responsiveness in particular, and peripheral insulin resistance in glycemic control in various ethnic population.

The limitation of our study is its cross-sectional nature. Nevertheless, this constitutes the largest scaled study on the fasting and postprandial insulin secretion, which was examined by the meal tolerance test, in type-2 diabetic patients, whose duration of diabetes was varied. In summary, fasting and postprandial insulin secretions were found to decrease as the duration of diabetes was increased, and particularly, postprandial insulin secretion was more prominently decreased. Furthermore, in comparison with fasting β-cell responsiveness, postprandial β-cell responsiveness was observed to exert greater effect on glycemic control in type-2 diabetes mellitus.

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